UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/807,096	11/19/2001	Anke Rattenholl	1406/415	2974

25297 7590 01/15/2010

JENKINS, WILSON, TAYLOR & HUNT, P. A.
Suite 1200 UNIVERSITY TOWER
3100 TOWER BLVD.,
DURHAM, NC 27707

EXAMINER	
HAYES, ROBERT CLINTON	

ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
01/15/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/807,096	RATTENHOLL ET AL.	
	Examiner	Art Unit	
	Robert C. Hayes, Ph.D.	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8,20 and 26-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,20 and 26-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/7/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicant's amendment filed on 10/07/09 has been entered.

2. The rejection of claims 8, 20 & 26-28 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn due to the amendment of the claims.

3. Applicant's arguments filed 10/07/09 have been fully considered but they are not deemed to be persuasive.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. Claims 8, 20 & 26-29 stand rejected under 35 U.S.C. 102(b) as anticipated by Edwards et al (U.S. Patent 5,683,894), and as described on page 4 of the instant specification where Edwards is acknowledged as admitted prior art for describing the "whole prosequence", and for the reasons made of record in Paper NOs: 20050124, 20050706, 20060329, 20060913, 20080212, 20081001 & 20090604, and as follows.

Applicants re-iterate arguments on pages 5-6 of the response "that Edwards discloses no preparations that would be properly considered a 'pharmaceutical composition' by one of ordinary skill in he art", and that "the *in vitro* translated pro-NGF-beta solution taught in Example 2 of Edwards 'would therefore reasonably be purified to at least 90% purity based upon

this translation system' also fails to support the instant rejection", and cites *In re Robertson*. In contrast to Applicants' assertions, the issue remains that the claims recite "*comprising* a pharmaceutically acceptable carrier", which includes the pharmaceutically acceptable carrier, water, etc. Second, because no side-by-side comparison has been provided by Applicants to alternatively demonstrate that the *in vitro* translation system cannot produce products that are at least 90% pure, and because the scope of the currently claimed invention encompasses Edward's pro-NGF-beta preparation, Applicants' arguments remain not persuasive.

As previously made of record, it has been established by the courts that a product (i.e., the proNGF **product**) inherently possesses characteristics of that product (i.e., possesses any activity inherent to the protein which is derived from its amino acid sequence), and that:

"the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. Accordingly, since the issue in the present appeal is whether the prior art factor is identified or patently indistinct from that of the material on appeal, appellants have the burden of showing that inherency is not involved". *Ex parte Gray,* 10 USPQ 2d 1922 (1989); *In re Best,* 195 USPQ 430 (CCPA 1976).

Which Applicants have not provided. In addition, the court in *In re Crish*, 73 USPQ2d 1364 (Fed. Cir. 2004), also held that "… the [further] identification and characterization of a [previously known] prior art material… does not make it novel".

Lastly, it is noted that the courts have held that when the prior art product reasonably appears to be the same as that claimed, but differs by process in which it is produced, a rejection of this nature is eminently fair and the burden is upon the appellants to prove, by comparative evidence, a patentable difference (*In re Brown*, 173 USPQ 685 (1972)).

In summary, Edwards et al teach how to make a pharmaceutical composition comprising a recombinant pro-NGF-beta solution (e.g., cols. 5 & 7-9), which can also be "derived from

humans" (e.g., col. 4, lines 40-42), which inherently comprises SEQ ID NO: 4 and inherently is encoded by a nucleic acid comprising SEQ ID NO: 3 (i.e., as it relates to claims 20, 27, 28 & 29). In that Example 2 (col. 7) teaches *in vitro* translated proNGF (i.e., including proNGF from "*human*, murine, bovine; col. 4, line 41), which therefore would reasonably be purified to least 90% purity based on this translation system, the limitations of claim 8 are anticipated; absent evidence to the contrary. In that proNGF produced by such a procedure inherently has whatever activity it possesses based on its structural characteristics from which functional activity is directly derived, the limitations of claims 26 & 29 are also reasonably met.

As previously made of record, Edwards clearly teach recombinant "NGF-beta… administered as a pharmaceutical composition…" (col. 5, line 57-58). See col. 5, lines 49- col. 6, line 14). Edwards also teach "one may cleave and activate the pro-NGF-beta to the mature form either before *or after isolation from the expression host* [emphasis added]"; thereby, demonstrating disclosure of an isolated pro-NGF-beta solution (col. 5, lines 17-19). Example 5 (in column 5) discloses "pro-NGF-beta *prepared in vitro* as described in Example 2 above was substituted for pro-NGF-beta prepared *in vivo*" (col. 8, lines 38-40 & 44-46). Column 8 (lines 60) discloses "[p]ro-NGF-beta *purified* from mouse L929… [emphasis added]". Column 9 discloses expression of "pro-NGF-beta in yeast for large scale fermentation" (col. 9, lines 16-39). Example 2 (in column 7) discloses preparation of "mouse pro-NGF-beta using an in vitro expression system, for comparison with active NGF-beta…" (col. 7, line 7-8). Simply put, as long as Edwards teach their pro-NGF-beta in solution that comprises the pharmaceutically-acceptable carrier water, etc., the limitation of a pharmaceutical preparation are met; especially when claim 8 recites the open claim language of "[a] pharmaceutical composition

comprising….". *In arguendo*, a pharmaceutical composition could also contain ^{35}S-methionine", especially when one wants to image, detect, etc. whether their "mouse pro-NGF-beta" became bound to the appropriate cells.

6. Claims 8, 20 & 26-29 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Gray & Ullrich (U.S. Patent 5,169,762) and Collins et al (U.S. Patent 5,235043), for the reasons made of record in Paper NOs: 20080212, 20081001 & 20090604, and as follows.

Applicants argue on pages 6-9 of the response that "applicants respectively traverse the Patent Office's assertion that the teachings of Edwards are not relevant to the instant rejection", based on the incorrect assumption that "Edwards' specific disclosure that pro-NGF is biologically inactive *per* se". In contrast to Applicants' unfortunate misrepresentation of the record, this is a rejection over Gray & Ullrich (U.S. Patent 5,169,762) and Collins et al (U.S. Patent 5,235043); not a rejection over Edwards, wherein attempts to argue that any prior art's pro-NGF preparations are "biologically inactive *per* se" simply cannot be supported by taking a passage out of context from a single reference (i.e., Edwards), which is further not part of the pending rejection.

In contrast, the issue remains that MPEP 2112 makes clear that:

> "The express, implicit, and inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. 102 or 103. "The inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness." In re Napier, 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir. **1995)** (affirmed a 35 U.S.C. 103 rejection based in part on inherent disclosure in one of the references). See also In re Grasselli, 713 F.2d 731, 739, 218 USPQ 769, 775 (Fed. Cir. 1983)."

Additionally, MPEP 2112 states that:

> "Where applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection. "There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102." In re Best, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977)."

Applicants then argue that "the apparent assertion [by the Examiner] that proNGF is a 'known, equivalent element' is clearly incorrect as it is only in the instant specification that proNGF is disclosed to have any activity at all. Thus, there is no disclosure in any reference cited by the Patent Office that would have led one of ordinary skill in the art to conclude that proNGF is an 'equivalent' of NGF". In contrast to Applicants' assertions, as illustrated by the teachings of Collins et al., recombinant production of biologically active proteins, wherein in particular "the proper folding and assumption of biological activity of mature NGF will only occur if it is first synthesized as the full-length precursor (i.e., as a proneurotrophin, such as proNGF), as occurs in eukaryotic cells and in natural sources" was well known in the art at the time of filing Applicants' invention; and where *in vitro* production of biologically active polypeptides was also routinely done in the art, as illustrated by the *in vitro* translation kits available from a number of companies (even though this is not part of the pending rejection). Moreover, 35 U.S.C. 282 makes clear that "every U.S. patent is presumed valid"/enabled, which therefore includes **Gray & Ullrich** (U.S. Patent 5,169,762) **and Collins et al** (U.S. Patent 5,235043), which is the prior art this rejection is based upon.

Applicants then argue that proNGF is not an equivalent of NGF, which simply is not correct, because proneurotrophic factors are well known to be the precursors of neurotrophic factors, such as proNGF is the precursor of NGF-beta. Accordingly, as taught by Collins, it is

well known in the art that proNGF is first made and then naturally processed into the mature NGF-beta form, which therefore reasonably and inherently would itself possess the functional activity of NGF-beta, which is well known in the art to "increase DRG [sensory] neuronal survival, as further supported by the teachings of Gray and Ullrich. By analogy, it is the Examiner's position that prodrugs that are metabolized into drugs are 'equivalants', and add no additional contribution to the art; absent evidence to the contrary, which Applicants have only attempted to support by a single passage taken out of context from a single reference (i.e., Edwards), while ignoring the other teachings made of record. Nonetheless, the analysis previously made of record remains consistent with the Supreme Courts holdings in *KSR International Co. v. Teleflex, Inc.* previously made of record. Thus, Applicants' arguments remain not persuasive, because their claims simply do not structurally distinguish their proNGF preparation from that *prima facie* obvious based on the teachings of **Gray & Ullrich** (U.S. Patent 5,169,762) **and Collins et al** (U.S. Patent 5,235043).

In regards to Applicants' arguments that each of the individual references not teaching the claimed invention, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In addition, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Lastly, Applicants are again reminded of that held by the Supreme Court in *KSR International Co. v. Teleflex Inc.* (82 USPQ2d 1385 (2007)), in which the simple substitution of one known, equivalent element [i.e., proNGF for NGF] for another to obtain predictable results [i.e., increase DRG neuronal survival], or the combining of prior art elements [i.e., Collins' proneurotrophin polypeptides for the proNGF polypeptide] according to known methods [of making recombinant polypeptides] to yield predictable results [i.e., increase survival of DRG neurons], reasonably supports a *prima facie* case of obviousness, especially given a finite number of predictable solutions [i.e., increased survival of DRG neurons using molecules that comprise the NGF amino acid sequence] where it would be obvious to try based on the teachings of Collins et al.

In summary, Gray et al teach both the amino acid and nucleotide sequence of human proNGF (i.e., Figs. 4-6; as it relates to claims 27-29). Gray also teach methods of making NGF proteins recombinantly using either prokaryotic or eukaryotic host cells (e.g., cols. 3-6; as it relates to claims 27 & 28), as well as pharmaceutical compositions thereof (e.g., col. 13; as it relates to claims 8, 20, 26 & 29). Although Gray et al are silent regarding the relative activity of proNGF as it relates to β-NGF, the activity of proNGF (or any polypeptide, in fact) is directly related to its structure (i.e., its amino acid sequence), and therefore, is an inherent property of proNGF (i.e., as it relates to claims 26 & 29). However, Gray et al do not specifically teach pharmaceutical preparations of purified human proNGF protein of at least 90% purity.

Collins et al teach "production of purified forms of all members of the NGF/BDNF family of neurotrophic proteins which would be valuable as pharmaceutical preparations" (e.g., col. 5), as well as biologically active recombinant human NGF family member proteins (e.g.,

cols. 5, 9-10, & 24; Figs. 6 & 7; as it relates to claims 8, 20 & 26-29). Although Collins et al are silent regarding the relative activity of proNGF as it relates to β-NGF, the activity of proNGF is directly related to its structure (i.e., its amino acid sequence), and therefore, is an inherent property of proNGF (i.e., as it relates to claims 26 & 29). Nevertheless, Collins et al teach that it was well accepted in the art that "the proper folding and assumption of biological activity of mature NGF will only occur if it is first synthesized as the full-length precursor (i.e., as a proneurotrophin, such as proNGF), as occurs in eukaryotic cells and in natural sources" (i.e., col. 32, lines 62-65); thereby, providing motivation for making human proNGF protein nonetheless. However, Collins et al do not specifically teach pharmaceutical preparations of purified human proNGF protein of at least 90% purity.

It would have been obvious to one of ordinary skill in the art to make and purify human proNGF to homogeneity based on the teachings of both Gray and/or Collins using standard purification techniques known in the art, or as described by both Gray et al, or by Collins et al. , etc. either for use in pharmaceutical compositions, as suggested by Collins, in which the subsequent purification would reasonably minimize undesirable side effects and/or adverse immunological concerns well known in the art (thereby, increasing the number of neurotrophic proteins valuable for treating neurodegenerative diseases, as suggested by Collins (e.g., col. 5)), or for use of human proNGF as a prodrug for its eventual processing into a biologically active and mature NGF form, whose biological activity is well characterized within the art.

As previously made of record, no product-by-process steps are recited in the current claims. Even if such steps were recited, the issue would then become that if the product in a product-by-process claim (i.e., proNGF) is the same as or obvious from a product of the prior art,

the claim is unpatentable even though the prior art product was made by a different process. *In re Thorpe,* 227 USPQ 964, 966 (Fed. Cir. 1985): *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983). It has further been established by the courts that a product (i.e., the proNGF product) inherently possesses characteristics of that product (i.e., possesses any activity inherent to the protein because of its amino acid sequence), and that:

> "the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. Accordingly, since the issue in the present appeal is whether the prior art factor is identified or patently indistinct from that of the material on appeal, appellants have the burden of showing that inherency is not involved". *Ex parte Gray,* 10 USPQ 2d 1922 (1989); *In re Best,* 195 USPQ 430 (CCPA 1976).

The court in *In re Crish*, 73 USPQ2d 1364 (Fed. Cir. 2004), also held that "… the [further] identification and characterization of a [previously known] prior art material… does not make it novel".

Lastly, it is noted that the courts have held that when the prior art product reasonably appears to be the same as that claimed, but differs by process in which it is produced, a rejection of this nature is eminently fair and the burden is upon the appellants to prove, by comparative evidence, a patentable difference (*In re Brown*, 173 USPQ 685 (1972)).

New Rejections Necessitated by Applicants' Disclosure of New Prior Art

7. Claims 8, 20, 26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over in view of Gray & Ullrich (U.S. Patent 5,169,762) and/or Collins et al (U.S. Patent 5,235043), and/or Boehringer Mannheim GMBH/Lang et al (JP 09-023883 (1/28/97); IDS Ref #3).

Gray et al. and Collins et al. are as described above.

Lang et al. teach an improved method of producing biologically active beta-NGF by solubilizing any insoluble aggregates obtained from expression in *E. coli* and using a pulse regenerating treatment/denaturation/renaturation involving a redox system selected from cystamine/cysteamine and cysteine in the presence of arginine (see Abstract). However, Lang et al does not teach producing biologically active pro-NGF using this same improved methodology.

It would have been obvious to one of ordinary skill in the art to make and purify human proNGF to homogeneity based on the teachings of both Gray and/or Collins using standard purification techniques known in the art, or as described by both Gray et al, or by Collins et al. , etc. or as taught by Lang et al., either for use in pharmaceutical compositions, as suggested by Collins, in which the subsequent purification would reasonably minimize undesirable side effects and/or adverse immunological concerns well known in the art (thereby, increasing the number of neurotrophic proteins valuable for treating neurodegenerative diseases, as suggested by Collins (e.g., col. 5)), or for use of human proNGF itself as a prodrug for its eventual processing into a biologically active and mature NGF form, whose biological activity related to increasing DRG/sensory neuronal survival is well characterized within the art.

It would have been further obvious to one of ordinary skill in the art to make and purify human proNGF itself as a prodrug using Lang's improved method of denaturation/ renaturation of NGF polypeptides, in order to maximize biological activity cost effectively, as taught by Lang et al., because proNGF is prodrug as it relates to NGF-beta, which would alternatively and naturally be processed into NGF-beta once administered to a patient, and/or have equivalent biological activity as NGF-beta, due to its overlapping amino acid sequence identity, with a reasonable expectation of success.

8. Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 10/07/09 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609.04(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (571) 272-0885. The examiner can normally be reached on Monday through Thursday from 9:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Stucker, can be reached on (571) 272-0911. The fax phone number for this Group is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Robert C. Hayes/
Primary Examiner, Art Unit 1649
January 11, 2010